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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference -- | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/CU99/00002 | International filing date (day/month/year) 19/07/1999 | Priority date (day/month/year) 17/07/1998 |
| International Patent Classification (IPC) or national classification and IPC C08F6/00 | | |
| Applicant CENTRO NACIONAL DE INVESTIGACIONES CIENTIFICAS (CN) | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

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|---|---|
| Date of submission of the demand 02/02/2000 | Date of completion of this report 01.11.2000 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 | Authorized officer DE LOS ARCOS, E Telephone No. +31 70 340 3573  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CU99/00002

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-31 as originally filed

Claims, No.:

1-6 as received on 01/08/2000 with letter of 31/07/2000

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

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2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | |
|-------------------------------|-----------------|
| Novelty (N) | Yes: Claims 1-6 |
| | No: Claims |
| Inventive step (IS) | Yes: Claims |
| | No: Claims 1-6 |
| Industrial applicability (IA) | Yes: Claims 1-6 |
| | No: Claims |

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

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The examination is being carried out on the **following application documents**:

Description, pages:

1-31 as originally filed

Claims, No.:

1-6 as received on 01/08/2000 with letter of 31/07/2000

Drawings, sheets:

1/6-6/6 as originally filed

Re Item IV

Lack of unity of invention

1. The claims as presently worded refer to **two** (2) different inventions, which are not so related as to form a single general inventive concept (Rule 13 PCT), namely:
 - i) Use in pharmaceutical solid forms of polymers derived from vinyl acetate having Mw, contents of remnant monomer, water, acidity and peroxide, as well as Tg and innocuousness according to claim 1, and procedures according to claims 2, 4 5 and (in part) 6.
 - ii) Use in pharmaceutical solid forms of vinyl acetate-vinyl alcohol copolymers containing less than 30 % (molar) of vinyl alcohol, contents of vinyl alcohol and water according to claim 2, as well as procedures according to claims 3 and (in part) 6.

This Authority has considered however, according to Rule 61.8 PCT and in view of the several unclarities found in the claims as filed (see Item VIII), not to invite the Applicants to pay further fees, provided that the Applicants will amend the structure of the claims as required in Item VIII below, and according to Art. 34(2)(b) PCT.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1 = FR-A-2 398 091

D2 = WPI/DERWENT, Abstract No. 1980-61151C; & JP-A-55 092 655

D3 = BR-A-95 04636

D4 = CU-A-22199

2 The subject-matter of claims 1-6 appears to be novel (Art 33(2) PCT).

2.1 Document D1 differs from the process of claim 2 in that the molecular weight of the polymer is from 2500 to 6000 and the water content is not defined, see examples. These differences establish the novelty of claim 1 in view of D1 (Art. 33(2) PCT).

2.2 Document D2 differs from the process of claim 3 in that D2 does not specify the monomer or water content, or the PVAc/alcohol/alkaline hydroxide ratio. This establishes the novelty of claim 3 in view of D2 (Art. 33(2) PCT).

2.3 Document D3 discloses (see page 2, line 26 to page 5, line 8 and claims) PVAc polymers and uses thereof which differ from those claimed in claims 1 and 2 of the present application in that the total acidity, peroxide content and Tg are not specified. This establishes the novelty of claims 1 and 2 in view of D3 (Art. 33(2) PCT).

2.4 Document D4 discloses (see examples) uses of PVAc polymers and VAc-VOH copolymers which differ from those claimed in claims 1, 2, 5 and 6 of the present application in that the monomer content, total acidity, water content and peroxide content of the PVAc polymer or the monomer content, water content and peroxide content of the VAc-VOH copolymer is not disclosed. This establishes the novelty of claims 1, 2, 5 and 6 in view of D4

It follows that the subject-matter of claims 1-6 is novel in view of D1 - D4 (Art 33(2) PCT).

3 The subject-matter of claims 1-6 of the present application is not inventive for the following reasons:

3.1 Although D1 does not disclose explicitly the monomer and water content as claimed in claim 1, the general procedure of D1, see in particular example 1, refers to the elimination of residual monomers and reactants by washing the polymer three times with hot water, to the elimination of the water content of the polymer by drying it under vacuum to constant weight and to its recovery in molten state.

Polymers having molecular weights within the range claimed in claim 1 are known from D2. Document D2 also discloses a process which includes the elimination of water-soluble impurities with hot water.

Pure, non-toxic PVAc polymers, their preparation in solution (EtOH) and their use in pharmaceutical applications are known from D3.

Uses as those of claims 1 and 4-6 of the application are already known from D4.

Additionally, the application does not show (see examples and comparative examples on file) that the differences mentioned above could lead to any surprising or unexpected technical advantage other than those which are to be expected from the difference with respect to the purity of the polymers.

Thus the problem to be solved by the present application may be regarded as to provide further, different processes for preparing PVAc and/or VAc/VOH polymers, in view of D1-D4.

It seems obvious that the person skilled in the art, using common knowledge techniques, eg., such as those mentioned in the cited documents, in particular in D2 and D3, would arrive to any desirable degree of purity, and thus that the advantages so obtained would have been fully predictable.

It follows that the subject-matter of claims 1-6 is not inventive in view of cited documents D1-D4 (Art 33(3) PCT).

Re Item VII

Certain defects in the international application

1. It is clear from the description on page 1, lines 4-9, page 7, lines 1-10, page 14, lines 4-7, page 15, lines 4-24, page 16, lines 1-3, 10-15 and 21-33 and Examples that the following feature is essential to the definition of the invention:

- (1) The copolymers of vinyl acetate-vinyl alcohol with less than 30 (wt.) % vinyl alcohol monomeric units content **is obtained** from the claimed polyvinyl acetate and
- (2) The copolymers of vinyl acetate-vinyl alcohol with less than 30 % (molar?) vinyl alcohol monomeric units content has to fulfill all and the same purity requirements claimed for the polyvinyl acetate.

Since independent claims 1, 3, 4 and 6 do not contain this feature they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention (see also Item IV).

2. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

3. The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.

Re Item VIII

Certain observations on the international application

1. The following expressions used in claims 1, 3 and 5 are vague and unclear and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

1.1 In claim 1, the expression **less than 30 %**, since it does not refer to any basis.

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1.2 In claim 3, the expression "in **similar way** as is described under claim 2", since it is a merely illustrative technical feature which does not constitute any limitation to the claim.

1.3 In claim 5, the expression **or of granulates that contain active substances**, since it is not clear that the resulting expression **Procedures for use of granulates that contain active substances (...)** has a defined meaning in this context.
(Additionally, such as subject-matter cannot be found in the application as originally filed, Art. 19(2) PCT).

CLAIMS

- 1- Use of polymers derived from vinyl acetate in pharmaceutical solid forms characterized by
 - use of polyvinylacetate of mean molecular weight between 10000 and 40000 daltons, remnant monomer content less than 2 ppm by weight, water content less than 1.5 % by weight, total acidity referred to acetic acid less than 0,5 % by weight, peroxide content 0,0 %, glass transition temperature 35-39 °C, innocuous after oral ingestion;
 - use of copolymers of vinylacetate-vinyl alcohol with less than 30 % vinyl alcohol monomeric units content and the same vinylacetate and water content as above described for polyvinylacetate.
- 2- Procedure for the obtaining of polyvinylacetate, with mean molecular weight, the purity requirements and innocuousness described under Claim 1, by polymerization of vinyl acetate in solution, preferably in ethanol, with use of dibenzoyl peroxide as initiator, subjected to a preliminary purification step by means of the addition of an adequate volume of hot water to a solution of the polymer (in ethanol or other volatile solvent), or by means of the addition of a solution of the polymer to an adequate volume of hot water (> 80 °C), during a time that depends on the employed equipment, on the mechanical stirring, and on the maintenance of a high temperature (> 80°C) of the resultant mass, with optionally bubbling of purified air through the said mass, until the achievement of the separation of the solvent by means of evaporation or dragging with help of the water vapor, the decomposition of the remnant initiator, the dissolution of the major part of the benzoic acid in water and the removal of the major part of the remnant monomer, the separation of the water phase from the semisolid humid polymer mass and the further purification of the said semisolid mass, being this purification and the handling of the final product characterized by
 - heating of the said mass at a temperature between 80 and 140 °C, under vacuum (0.02-13 kPa), and stirring the mass slowly until the polymer presents the desired purity and dryness;

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- evacuating molten the purified polymer from the purification equipment.
- 3- Procedure for the obtaining of vinyl acetate-vinyl alcohol copolymers with the characteristics described under Claim 1 by means of alkaline alcoholysis/hydrolysis of polyvinylacetate of high purity, characterized by
- the use of an alcohol, preferably ethanol, as solvent, and the fixing of a ratio between the initial quantities (by weight) of polyvinylacetate/ alcohol/ alkaline hydroxide within the range of ratios that, following the same order, is expressed in the ratio: 50-80 / 130-170/ 1;
 - the addition of water to the initial reaction mixture in such quantities that it constitutes between 4 and 25% by volume of the solvent present;
 - being performed the final purification of the copolymer in similar way as is described under Claim 2.
- 4- Procedure for the obtaining of polyvinylacetate and of vinyl acetate-vinyl alcohol copolymers as a powder, stable enough in its storage and useful in preparations of compressed tablets obtained by direct compression or by means of previous wet granulation, characterized by
- use of polyvinylacetate with mean molecular weight, the purity requirements and innocuousness described under Claim 1, as starting material;
 - being performed the procedure in three steps, the first of which is the milling of the said polymer in a cutting or hammer mill, using a sieve with hole dimensions between 2.5 and 0.8 mm; the second step is the mixing of the gross grained polymer, obtained in the described first step, with pharmaceutical crystalline excipients of small particle size (preferably lactose) or with a crystalline active substance, being the said substance 30-80 weight % of the total mixture, followed by the milling of the mixed solid in the same kind of mill using a sieve with hole dimensions between 0.2 and 0.04 mm; the third step is the homogenizing mixing of the milled product.
- 5- Procedures for use of polyvinylacetate as binder in base granulates or of granulates that contain active substances, being the said procedures characterized by

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- use of polyvinylacetate with mean molecular weight, the purity requirements, dryness and innocuousness described under Claim 1, as the only or principal binder;
 - use of said polyvinylacetate as solid powder intimately mixed with lactose or with other crystalline excipient, obtained by the procedure described under Claim 4, for the obtaining of granulates by means of moistening with acetone, ethanol or other appropriate solvent, or use of said polymer in a solution with an organic convenient solvent;
 - use of said polyvinylacetate in a quantity that represents between 1 and 10 % by weight of dried granulates.
- 6- Procedures for use of polyvinylacetate or vinyl acetate-vinyl alcohol copolymers with mean molecular weight, the purity requirements, dryness and innocuousness described under Claim 1 as simultaneous binders and sole or main constituents of release controlling matrixes (> 60 weight % of the polymeric matrix and between 2 and 25 weight % of the pharmaceutical solid form) in compressed tablets and pellets being the said procedures characterized by the fact that the occlusion of the active substance, the drug or the releasing substance in general, within the matrixes of the said polymers takes place by either one of the following ways;
- depositing the polymer on one, several or all the components of the formulation by wetting them with a polymer solution, evaporating thereafter the solvent, granulating and optionally compressing the mixture with addition or not of other excipients as fillers or lubricants,
 - intimate mixing of the polymer as powder or as granulate, obtained by the procedure described under Claim 4, with active substance or drug, solid or liquid, supported in the latter case on an inert solid, granulating the mixture if necessary by means of humectation with a solvent of the polyvinylacetate and compressing the said mixture with addition or not of other excipients as fillers or lubricants.

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